REMARKS

The Office rejected claims 23-32 under 35 U.S.C. § 101, for allegedly being directed to non-statutory subject matter, and under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description. Claims 23-26 were rejected under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. In addition, the Office rejected claims 27 and 30-32 under 35 U.S.C. § 102(g) as allegedly anticipated by U.S. Patent Publication 2003/0192078 (Fischhoff et al.) ("the '078 publication"), which is a divisional of U.S. Patent Application No. 08/434,105. Finally, claims 23-32 were rejected on the ground of non-statutory obviousness-type double patenting for allegedly being unpatentable over claims 1-3 of U.S. Patent 6,833,449 ("the '449 patent"). Reconsideration is respectfully requested.

I. The Objections To The Claims Are Moot.

The Office objected to claims 23-27 for assertedly containing informalities. (Action at page 2.) The objection to claims 23-26 is moot because these claims are cancelled. Claim 27 was amended to include "said method" (as suggested by the Examiner), rendering moot the objection to claim 27.

II. Amendments to the Specification, Figures, and Claims

The figure descriptions in the specification have been amended to incorporate language entered in U.S. Patent Application No. 10/394,548 (now U.S. Patent 6,833,449) by way of an Examiner's Amendment. U.S. Patent Application No. 10/394,548 is a continuation of the instant application. The amendments to the figure descriptions are supported by the Figures and Examples. The amendments also correlate the nucleic acid sequences recited in the figures with sequence identifiers recited in the Sequence Listing submitted herewith.

Many of the claim amendments merely address matters of form or adopt implicit or explicit suggestions from the Examiner for eliminating objections or rejections. Some of the amendments merely improve the way that steps of the method relate to each other. No new matter has been introduced.

Claims 23-26 have been cancelled.

The amendment to claim 27 is supported by the specification at, e.g., page 3, lines 24-30; page 4, lines 10-13; page 9, lines 30-35; page 10, lines 6-17; page 15, lines 20-32; and the Example. Claims 28, 31, and 32 have been amended to standardize the language used throughout the claims. Claim 31 also has been amended to adjust the dependency of that claim.

Claim 29 has been amended to state that "modifying comprises substituting the highest frequency codon for at least 59 amino acids," as supported by the specification at, e.g., page 9, line 30, through page 10, line 30, previous claims 23 and 25, and existing claims 27 and 28. The amendment to claim 30 is supported by the specification at, for example, page 11, lines 17-24.

Support for new claims 33-44 can be found in the specification at, for example, page 3, lines 24-30; page 9, lines 30-35; page 10, lines 6-17; page 11, lines 17-24; page 12, lines 6-29; page 13, lines 7-26; and page 15, lines 20-32.

III. The Rejection Under Section 101 Should Be Withdrawn.

The Office rejected claims 23-32 under Section 101 for allegedly being directed to non-statutory subject matter. (Action at pages 2-3.) According to the Office, a method comprising modifying a coding sequence does not require any physical transformation of matter. Applicants respectfully disagree with the Office's position. However, solely in an effort to advance prosecution of the application, claim 27 has been amended to specify that a nucleic acid is modified or constructed (a physical transformation of matter). Claims 28-32 depend from claim 27. Claims 23-26 have been cancelled. Thus, the rejection is moot, and should be withdrawn.

IV. The Rejection Under Section 112, First Paragraph, Should Be Withdrawn.

Claims 23-32 were rejected under Section 112, first paragraph, for allegedly encompassing subject matter that is not described in the specification so as to reasonably convey to one of ordinary skill that Applicants had possession of the claimed invention as of the effective filing date of the application. (Action at pages 3-4.) The applicants respectfully traverse.

The written description requirement is satisfied when the specification describes the claimed invention in sufficient detail to allow one skilled in the art to recognize that the applicants invented what is claimed. *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319 (Fed. Cir. 2003). As explained below, the instant specification supports the full scope of the pending claims, thereby meeting the requirements of Section 112, first paragraph.

A. The application conveys that the invention was considered applicable to any B.t. insecticidal protein coding sequences.

In the rejection of claims 23, 25, and 31, the Office asserts that only a method of modifying the native coding sequence for a *B.t.* delta-endotoxin is described, and not a method of modifying other *B.t.* insecticidal protein coding sequences.

To the contrary, the specification makes clear that the method of the invention is applicable to a wide variety of coding sequences for expression in plants, and is particularly applicable to *B.t.* coding sequences generally. For example, the application states that the invention is applicable to any "foreign gene to be expressed in plant cells." (See Summary of Invention, page 3, lines 24-30.) (Compare new claim 33.) The application also explicitly states that, although the disclosure focuses on a *B.t.* delta endotoxin, the method is "equally applicable to other prokaryotic or even eukaryotic, genes which happen not to express well in plants. . . Other prokaryotic or eukaryotic genes which similarly use a large number of codons which are not among those preferentially expressed by plants may also be altered" in accordance with the inventive method. (Specification at page 12, lines 7-12 and 16-20.) (Compare new claim 34.) The specification also teaches that "it is possible to express *many foreign proteins* effectively and efficiently in plant cells and still [] produce a protein identical in amino acid sequence to the native protein." (Specification at page 12, lines 24-29 (emphasis added).) (Compare new claim 33.) The specification also discloses that the inventive method "may even be applicable to some plant genes . . . to enhance the level of a native plant gene by similarly changing the pattern of its codon usage." (Specification at page 12, line 30, through page 13, line 2.) Based on the above passages, one of ordinary skill in the art would not conclude that that the invention was limited to *B.t.* delta-endotoxin, which merely represents "an example" of a foreign gene that is expressed poorly in plant cells. (Specification at page 2, lines 19-23.)

The application also conveys that the Applicants considered the inventive method to be particularly applicable to protein coding sequences, including insecticidal protein coding sequences, from *B.t.* In this regard, Applicants note that claim 31 does not refer to a *B.t.* insecticidal protein as suggested by the Office, but to a *B.t. coding sequence.* (Compare new claim 35.) The application points to *B.t.* as being particularly amenable to genetic modification (according to the invention) to enhance protein production in plants. The specification teaches that a problematic feature found in all reported *B.t.* genes is a high proportion of adenine and thymine (A+T) bases. (Specification at page 5, lines 12-21.) The application also discusses the invention with regard to *B.t.* when characterizing the product of the method, "it was . . . possible to construct a synthetic *B.t.* coding region for a chimeric gene composed principally of codons selected from those codons which are preferentially expressed by plants." (Specification at page 9, lines 30-35). The application teaches that the inventive method is applicable to any plant species capable of transformation, and that plants expressing a synthetic insecticidal sequence constructed in accordance with the inventive method exhibited uniform and enhanced insect toxicity. (See specification at, e.g., page 11, line 17, through page 12, line 6; and page 19, lines 11-19.)

From these passages, a reader would have appreciated that the invention was generally applicable to any heterologous protein contemplated for plant expression and particularly applicable to *B.t.* proteins, such as *B.t.* insecticidal proteins. Thus, the rejection was improper, and should be withdrawn.

The same analysis confirms that the method is adequately described with respect to each genus of coding sequence recited in new claims 33-44.

B. Substituting plant-preferred codons for those encoding at least the first 25 amino acids or at least the first 59 amino acids of a coding sequence is described by the application.

The Office further asserts that the specification fails to support modification of "at least the first 25 amino acids" in a coding sequence and, instead, only describes modifying "about 25 codons" at the N-terminus. On the contrary, it is clear from the specification that the Applicants contemplated substituting at least the first 25 amino acids as an embodiment of the invention. The application teaches that expression enhancement is due principally to substitutions at the amino-terminus of the coding sequence, i.e., substitutions of

about the first 25 codons, with high frequency codons. (Specification, page 13, lines 11-16.) Applicants also teach "[p]erforming such a codon substitution for the *remaining portion of the coding region* [i.e., beyond the first 25 codons] *might still be expected to increase efficiency of expression*." (Specification, page 13, lines 11-16 (emphasis added).) The application conveys that the inventors considered substitution of the first 25 amino acids to be a preferred embodiment of the invention and that additional substitutions beyond the first 25 amino acids could also enhance expression. Specific examples involved, e.g., 59 changes or 138 changes, and it is very clear to the reader that the teaching to modify as few as about the first 25 codons is a general teaching – not limited to a specific sequence in the examples. Thus, the application adequately describes the variation of the invention wherein highest frequency codons are substituted for at least the first 25 amino acids of the native coding sequence. New claim 33 includes this feature.

The Office also contends that the discussion in the specification about modifying 59-138 codons was limited to a specific *B.t.* sequence used in the Examples, and that the specification does not support a claim limitation specifying these number of changes to any coding sequence. The passages in question are not part of the Examples, but are a discussion/analysis of the Examples and lessons to be learned from the Examples. As such, the specification conveys that Applicants considered this number of modifications of a coding sequence for other sequences, not just for specific sequences in the Examples.

For these reasons, the rejection of claims 28 and 29 under Section 112, first paragraph, should be withdrawn. The rejection likewise is inapplicable to new claim 40, which contain the phraseology that the Examiner acknowledges to have literal written descriptive support.

C. *The rejection of claim 30 relating to "at least one regulatory sequence" is moot.*

The Patent Office alleged inadequate support for "attaching a single regulatory sequence" to a modified sequence, even though the specification explicitly "provides support for attaching flanking regulatory sequences ...." The Patent Office appears to be applying an *ipsis verbis* or *in haec verba* (word-for-word) standard for written description, which is clearly improper according to the PTO's reviewing court. *E.g., Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1364 (Fed. Cir. 2003). The proper standard pertains to what a

person of ordinary skill would understand from the application. M.P.E.P. § 2163. Notwithstanding, claim 30 has been amended to specify the language that the Patent Office identified as having literal basis in the application, rendering moot the rejection, which, should be withdrawn.

The rejection likewise is inapplicable to new claims 38, 39, and 46, which contain the phraseology that the Examiner acknowledges to have literal written descriptive support.

V. The Rejections Under Section 112, Second Paragraph, Should Be Withdrawn.

The Office rejected claims 23-26 under Section 112, second paragraph, for allegedly being indefinite for issues relating to lack of antecedent basis and for use of an abbreviation without including (in the claim) the term being abbreviated. (Action at page 4.) The rejection is moot in view of the cancellation of claims 23-26.

VI. The Rejection Under Section 102(g) Should Be Withdrawn.

The Office rejected claims 27 and 30-32 under Section 102(g) for allegedly being anticipated by the '078 publication, which is a published divisional of U.S. Patent Application No. 08/434,105 (currently pending). The instant patent application and the '105 application were involved in Interference No. 103,781. The Board of Patent Appeals and Interferences awarded priority to Party Fischhoff (the '105 application) with respect to the subject matter of the count of the interference.[1] Based on the decision, the Office contends that, in December 1986, Fischhoff reduced to practice "a method of designing a synthetic Bacillus thuringiensis gene, said method comprising modifying the native sequence by substituting at least some of the codons in the native coding sequence with codons for the same amino acids but that have the highest frequency in instant Table 1." (Office Action, page 5, § 11.) The applicants respectfully traverse this rejection.

[1] The parties in the interference were Adang and Fischhoff and Barton. Monsanto, one of the real parties in interest, owns both the Fischhoff and the Barton applications. Monsanto selected the Fischhoff application for the *inter partes* interference and prevailed at the Board against Adang.

The '078 publication anticipates the pending claims under Section 102(g) *only* if the reference teaches *each and every element* of the pending claims. See, e.g., *Standt Tech., Ltd. v. Resco Metal & Plastics Corp.*, 264 F.3d 1344, 1350 (Fed. Cir. 2001).

Amended claim 27 specifies a method that comprises modifying a native coding sequence by substituting, for codons in the native coding sequence, ***only*** codons for identical amino acids that have the highest frequency of use in plant genes according to the plant codon usage table in Figure 1. The '078 publication does not disclose each and every feature of the pending claims inasmuch as some of the highest frequency codons identified in Figure 1 of the present application are different than the codons disclosed in the '078 publication as having the highest percent usage in plants, and some of the substitutions in Fischhoff's examples involve the "different" codons. *Eight* of the twenty codons (*40%*) described in the '078 publication as having the highest percent usage in plants are different than those listed as highest frequency codons in instant Figure 1, as highlighted in the table below.

	Highest frequency codon in '078 publication	Highest frequency codon in instant Figure 1
Arginine	AGA	CGC
Leucine	UUG	CTC (CUC)
Serine	UCC	AGC
Alanine	GCU	GCC
Glycine	GGU	GGC
Valine	GUU	GTG (GUG)
Glutamine	CAA	CAG
Aspartate	GAU	GAC

The existence of *some* overlap between codons identified in the '078 publication and instant Figure 1 is not sufficient to maintain an anticipation rejection. The Fischhoff reference does not teach a method wherein substituted codons *only* are codons that encode the same amino acid and are the codon of highest frequency of usage in plants according to the different codon table in Figure 1 of the present application. Accordingly, the rejection of claims 27 (and dependent claims 30-32) under Section 102(g) should be

withdrawn. (For similar reasons, the basis for rejection is inapplicable to new claims 38-39, which specify that each substitution consists of a codon used in the highest frequency in plants recited in Figure 1.)

VII. The Rejection For Alleged Non-Statutory Obviousness-Type Double Patenting Should Be Withdrawn.

The Office rejected claims 23-32 for non-statutory obviousness-type double patenting for allegedly being unpatentable over claims 1-3 of the '449 patent. Claims 23-26 have been cancelled. Claims 1-3 of the '449 patent are directed to nucleic acids encoding a toxic portion of Cry1A, wherein codons of the nucleic acid are selected from codons described in Figure 1 as being used at the highest frequency in plants. The Office contends that the nucleic acid makes obvious a method of making a coding sequence for a *B.t.* endotoxin using the highest frequency codons identified in Figure 1. The Applicants respectfully traverse the rejection.

A double patenting analysis does not consider what someone may recognize by reading the claim language. Instead, the claims are "looked to solely for the purpose of determining what has already been patented." See *In re Sutherland*, 347 F.2d 1009, 1015 (C.C.P.A. 1965). In establishing the obviousness-type double patenting rejection, the Office inappropriately considered what the words of the claims of the '449 patent *disclose*, instead of what invention the claims *define*. *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1280-81 (Fed. Cir. 1992) ("Our precedent makes clear that the *disclosure* of a patent cited in support of a double patenting rejection cannot be used as though it were prior art, *even where the disclosure is found in the claims*." (emphasis in original)). The Office's incorrect analysis is highlighted by the last sentence of the rejection: "*As the method steps are the same*, methods of increasing the level of efficiency in expression of a Bt insecticidal protein are also made obvious" by the nucleic acid claimed in the '449 patent. (Office Action, page 6, § 13 (emphasis added).)

Claims 1-3 of the '449 patent define an invention that is a nucleic acid (i) encoding a toxic portion of a Cry1A protein and (ii) comprising particular codons. A nucleic acid is a *product*, not a method, and a nucleic acid product does not generally teach or suggest the method by which its sequence was selected or the method by which it was made.

More specifically, the nucleic acid defined by the claims of the '449 application does not render obvious the method of claim 27 (or claims 28-32 dependent thereon), which entails modifying a native *B.t.* coding sequence by substituting, for codons encoding an amino acid, only codons selected from Figure 1 that are used in the highest frequency in plants.

Although the claims of the '449 patent make reference to codons set forth in Figure 1 of the patent, and the method claims pending in this application specify using codons in Figure 1, this observation is an observation about what is *disclosed by* the claims, rather than what is *defined by* the claims. However, as the Patent Office's reviewing court has repeatedly said, it is not proper to analyze the prior patent's claims for what the words suggest. Rather, the exercise involves considering the words to determine what invention they define, and then determining whether the invention anticipates or renders obvious the pending claims. The Patent Office has failed to articulate why the product claimed in the cited patent anticipates or renders obvious any of the present claims relating to a method of making a product. The rejection should be withdrawn.

Furthermore, it appears that the Office applied an erroneous "one-way" test in rejecting the claims for obviousness-type double patenting. The Office's analysis was limited to whether the claims of the instant application are allegedly unpatentable in view of certain claims of the '499 patent. However, a "two-way" test is appropriate in circumstances wherein prosecution of an earlier application is delayed in the PTO, causing a later-filed application to issue before the earlier-filed application. See *In re Braat*, 937 F.2d 589, 593 (Fed. Cir. 1991). Here, issuance of the instant application has been delayed by an interference declared by the Board of Patent Appeals and Interferences. The issued patent was filed after the instant application, but issued first as a consequence of the prosecution delay caused by the interference. Accordingly, the Office should have used a "two-way" test, wherein (a) an application claim must be an obvious variant of a '499 patent claim and (b) the '499 patent claim must be an obvious variant in view of the application claim to support a rejection for obviousness-type double patenting. *In re Emert*, 124 F.3d 1458, 1461 (Fed. Cir. 1997). The Patent Office has not alleged or established that claims of the '499 patent, which are directed to nucleic acids encoding a toxic portion of Cry1A from a particular *B.t.* species, are obvious in view of the instant method claims.

VIII. Conclusion

In view of the above amendment, Applicants believe that the pending application is in condition for allowance. The Examiner is invited to contact the undersigned attorney by telephone if there are issues or questions that might be efficiently resolved in that manner.

Dated: November 18, 2008

Respectfully submitted,

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